



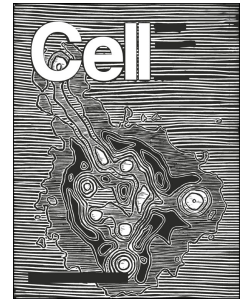
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Journal Pre-proof

COVID fog demystified

Jennifer Kao, Paul W. Frankland



PII: S0092-8674(22)00725-5

DOI: <https://doi.org/10.1016/j.cell.2022.06.020>

Reference: CELL 12522

To appear in: *Cell*

Please cite this article as: Kao, J., Frankland, P.W, COVID fog demystified, *Cell* (2022), doi: <https://doi.org/10.1016/j.cell.2022.06.020>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Published by Elsevier Inc.

COVID fog demystified

Jennifer Kao^{1,2} and Paul W Frankland^{1-5,*}

¹ Program in Neurosciences & Mental Health, Hospital for Sick Children, 686 Bay St, Toronto, ON M5G 0A4, Canada

² Department of Physiology, University of Toronto, Toronto, ON M5G 1A8, Canada

³ Department of Psychology, University of Toronto, Toronto, ON M5S 3G3, Canada

⁴ Institute of Medical Sciences, University of Toronto, Toronto, ON M5S 1A8, Canada

⁵ Child & Brain Development Program, Canadian Institute for Advanced Research, Toronto, Ontario M5G 1M1, Canada

*Correspondence: paul.frankland@sickkids.ca

Acute mild respiratory COVID-19 infection can lead to a more chronic cognitive syndrome known as "COVID fog". New findings from Fernandez-Castaneda et al reveal how glial dysregulation and consequent neural circuit dysfunction may contribute to cognitive impairments in long COVID.

More than two years since the first detected cases of SARS-CoV-2, the virus continues to evolve new variants, infect hundreds of millions of people, and pose both acute and chronic threats to global health. In most infections, a patient's symptoms resolve within two weeks. However, recovery from initial infection is not always straightforward. In a significant fraction of patients, symptoms can persist for several months. This syndrome—which has become known as 'long COVID'—may occur even following initially mild cases (that is, those not requiring hospitalization) and can include significant cognitive dysfunction.

Initial awareness of long COVID emerged from anecdotal accounts, shared by patients on social media platforms such as Twitter, Facebook and Slack (Callard and Perego, 2021). Since then, a large number of studies have used more formal methods to catalogue the nature and frequency of long COVID symptoms. Within the cognitive domain, as many as one in four patients experience a range of symptoms that have become known colloquially as 'COVID fog', which includes problems in attention, language fluency, processing speed, executive function, and memory (Becker et al., 2021).

Given the sheer scale of infections, there is a pressing need to understand how cognitive dysfunction emerges in long COVID. A new paper in *Cell* by Fernandez-Castaneda and colleagues (2022) begins to address this need. Using mice as a model, they expressed human ACE2, the viral entry receptor required for successful COVID infection. Because ACE2

expression was restricted to the trachea and lungs, these mice developed only a mild form of the disease that was limited to the respiratory system and largely cleared within a week following intranasal inoculation with SARS-CoV-2 virus.

As a starting point, the researchers noted the striking similarities between COVID fog and another cognitive syndrome known as ‘chemobrain’. Chemobrain (or cancer therapy-related cognitive impairment, CRCI), is a neuroinflammatory condition that patients often experience following radiation or chemotherapy. In CRCI, elevations in neurotoxic cytokines and reactive microglia (brain-resident macrophages) lead to cascades of multicellular events that impact forms of both grey and white matter plasticity that are important for healthy cognition (Gibson and Monje, 2021).

Adopting this framework, the authors quantified changes in cytokines and microglial/macrophage reactivity following SARS-CoV-2 infection. Reminiscent of CRCI, they found that microglial/macrophage reactivity was elevated in subcortical and hippocampal white matter in mice following mild respiratory COVID. Remarkably, this elevation was persistent and still evident even seven weeks post-infection. Outside of the brain, they detected elevated cytokine levels in the cerebrospinal fluid and serum of mice. Although levels of many cytokines were altered, one in particular grabbed their attention. CCL11 remained persistently elevated in mouse cerebrospinal fluid seven weeks post-infection. Notably, elevated CCL11 levels have been causally linked to cognitive impairments observed in normal aging (Villeda et al., 2011).

Similar patterns were found in patients with COVID-19. Reactive microglia were elevated in subcortical white matter in individuals with COVID-19 (these patients were symptomatic for COVID-19 but died from other causes). Moreover, CCL11 was elevated in plasma from patients with long COVID. Remarkably, elevated CCL11 plasma levels were only detected in those long COVID patients with cognitive symptoms. CCL11 plasma levels were unaltered in long COVID patients that did not have cognitive symptoms. These findings suggest that CCL11 plays a central role in the brain pathology contributing to COVID fog.

There are several ways in which such a neuroinflammatory state might impact cognition. Previous work has shown that persistently reactive microglia in hippocampal white matter suppress hippocampal neurogenesis by blocking neuronal progenitor-cell differentiation into new granule cells (Monje et al., 2003). These newly generated neurons are important for the formation and stability of hippocampus-dependent memories. The authors found the numbers of new neurons were reduced in infected mice, and this reduction correlated with numbers of reactive microglia in the hippocampus. Remarkably, systemic administration of CCL11 recapitulated this same pattern in uninfected mice. Increased numbers of reactive microglia and decreased numbers of new neurons in these mice suggest a causal role for CCL11 in COVID fog pathology. These CCL11-induced outcomes were restricted to the hippocampus, suggesting that particular cytokines can have circuit-specific effects.

Another way in which CCL11 and/or reactive microglia might impact cognition is via effects on white matter. In CRCI, reactive microglia impair the formation of myelin-forming oligodendrocytes and myelin plasticity (Geraghty et al., 2019; Gibson et al., 2019). Similarly, the authors found reduced numbers of oligodendrocytes and their precursor cells, as well as decreased axon myelination in the subcortical white matter, several weeks following infection in mice. Although behavior was not assessed in this study, it is nonetheless reasonable to assume that such changes would alter cognitive function following mild respiratory COVID in mice, as it

does in other disease contexts (Geraghty et al., 2019; Gibson et al., 2019). Since myelination regulates the speed and timing of communication between neurons, dysregulation of oligodendroglial lineage cells following infection might slow neural processing, disrupt brain synchrony, and impair cognition (Steadman et al., 2020).

The principle that inflammatory challenges may induce glial dysregulation and consequent neural circuit dysfunction is not specific to COVID-19. Many systemic infections are associated with lasting cognitive impairments. For instance, similar to COVID-19, the Spanish flu of 1918 (caused by H1N1 influenza virus infection) was associated with ‘brain fog’. In the current study, the authors compared the effects of mild respiratory SARS-CoV-2 infection with a mouse model of mild respiratory H1N1 influenza. Similar to SARS-CoV-2 infection, they found persistently elevated CCL11 in the H1N1 influenza infection. Therefore, CCL11-driven neuroinflammatory changes and cellular deficits may represent a common pathway to cognitive deficits in both mild respiratory COVID-19 and H1N1 influenza disease (as well as perhaps in other contexts, including aging).

However, different systemic infections can also have non-overlapping outcomes. For instance, whereas risk for anxiety and depression appears to be elevated in COVID-19, Spanish flu was associated with increased prevalence of psychosis (Honigsbaum, 2013). What accounts for these differences? One clue emerges from the current study. While CCL11 was elevated following SARS-CoV-2 and H1N1 influenza infection, a subset of cytokines was differentially regulated in these two conditions. It is likely that these non-overlapping cytokines (and their potentially non-overlapping circuit effects) might differentiate these diseases in terms of elevated risks for particular neuropsychiatric outcomes.

If cytokines have circuit-specific effects, should we consider cytokine profiling as a way to inform our treatment strategies for viral-induced/non-viral induced cognitive syndromes? Future research will no doubt address this, and other outstanding questions. For instance, how are these effects mitigated by vaccination, administered before or after infection? And, perhaps most significantly, might interventions that block inducers of these cytokines or reset reactive microglia prove useful in treating COVID fog?

Declaration of interests: The authors declare no competing interests

References

- Becker, J.H., Lin, J.J., Doernberg, M., Stone, K., Navis, A., Festa, J.R., and Wisnivesky, J.P. (2021). Assessment of Cognitive Function in Patients After COVID-19 Infection. *JAMA Netw Open* 4, e2130645.
- Callard, F., and Perego, E. (2021). How and why patients made Long Covid. *Soc Sci Med* 268, 113426.
- Fernández-Castañeda, A., Lu, P., Geraghty, A.C., Song, E., Lee, M.-H., Wood, J., O’Dea, M.R., Dutton, S., Shamardani, K., Nwangwu, K., et al. (2022). Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation. *Cell* 185, XXXX–XXXX.

Geraghty, A.C., Gibson, E.M., Ghanem, R.A., Greene, J.J., Ocampo, A., Goldstein, A.K., Ni, L., Yang, T., Marton, R.M., Pasca, S.P., et al. (2019). Loss of Adaptive Myelination Contributes to Methotrexate Chemotherapy-Related Cognitive Impairment. *Neuron* 103, 250-265 e258.

Gibson, E.M., and Monje, M. (2021). Microglia in Cancer Therapy-Related Cognitive Impairment. *Trends Neurosci* 44, 441-451.

Gibson, E.M., Nagaraja, S., Ocampo, A., Tam, L.T., Wood, L.S., Pallegar, P.N., Greene, J.J., Geraghty, A.C., Goldstein, A.K., Ni, L., et al. (2019). Methotrexate Chemotherapy Induces Persistent Tri-glial Dysregulation that Underlies Chemotherapy-Related Cognitive Impairment. *Cell* 176, 43-55 e13.

Honigsbaum, M. (2013). "An inexpressible dread": psychoses of influenza at fin-de-siecle. *Lancet* 381, 988-989.

Monje, M.L., Toda, H., and Palmer, T.D. (2003). Inflammatory blockade restores adult hippocampal neurogenesis. *Science* 302, 1760-1765.

Steadman, P.E., Xia, F., Ahmed, M., Mocle, A.J., Penning, A.R.A., Geraghty, A.C., Steenland, H.W., Monje, M., Josselyn, S.A., and Frankland, P.W. (2020). Disruption of Oligodendrogenesis Impairs Memory Consolidation in Adult Mice. *Neuron* 105, 150-164 e156.

Villeda, S.A., Luo, J., Mosher, K.I., Zou, B., Britschgi, M., Bieri, G., Stan, T.M., Fainberg, N., Ding, Z., Eggel, A., et al. (2011). The ageing systemic milieu negatively regulates neurogenesis and cognitive function. *Nature* 477, 90-94.

Figure 1: The neuroinflammatory basis of Covid fog.

Acute mild respiratory COVID-19 infection can lead to a more chronic cognitive syndrome known as "brain fog". Suggested pathways for brain fog include cytokine-induced activation of regional microglia, causing decreased hippocampal neurogenesis and a loss of myelinated subcortical axons.

